Method and system for registration, identifying and processing of drug specific data

BACKGROUND OF THE INVENTION

1. Field of the Invention

The invention relates to a method for registration, iden-
tifying and processing of drug specific data and for making
drugs available to individual patients avoiding adverse drug
reactions (ADR). The invention relates also to a system for
carrying out such a method.

2. Description of the Prior Art

Current methods and systems being used for access control
of drug delivery are not sufficiently reliable and secure for
the routine medical treatment of patients with drugs.

Thus, more than 2 million adverse drug reactions occur
annually in the United States. An analysis of 39 prospective
studies (JAMA 1998, 279, 1200-1205) shows that in 1994
2'216'000 patients have been hospitalised with adverse drug
reactions, 106'000 patients of them with fatal outcome.

Recent examples of drugs affected by severe ADR include the
following:

Drug	Reaction
Troglitazone Rezulin	Anti-diabetes type II drug; severe liver toxicity, unexpected deaths; Warning labelling introduced by FDA;

Drug	Reaction
	withdrawn from market.
Trovafloxacin Trovan	Antibiotic drug; unexpected severe liver toxicity with deaths occurring; call for ban of product that made US$ 68 Mio in its first year in the USA alone; boxed warning introduced by FDA.
Tolcapone Tasmar	Anti-Parkinson drug; severe liver toxicity with deaths; banned in UK, severely restricted in its use the in US.
Lazabemide Tempium	Anti-Alzheimer disease drug; severe liver toxicity in Phase III clinical trials; development aborted.
Sparfloxacin Zagam	Antibiotic drug; severe phototoxicity and cardiotoxicity; in EU limited to use in pneumonia.
Grepafloxacin Raxar	Antibiotic drug; severe cardiovascular events, several deaths; withdrawn from market.
Moxifloxacin Avelox	Antibiotic drug; FDA panel split about concerns on product safety; potential for prolonged QT-interval; approved.

SUMMARY OF THE INVENTION

The challenge of the invention is to develop a new system usable for a controlled drug development and personalised drug delivery.

It is the object of the invention to develop a new
sophisticated postgenomic knowledge management system which
links chemical molecular modelling, bioinformatic, genetic,
epidemiology, and molecular diagnostic data in order to de-
velop prospective theragenomic information which allows the
safe use of a given drug or a safe drug therapy, which is
free of severe adverse drug reactions in each individual
patient.

This object is achieved by a system for registration,
identifying and processing of drug specific data, which
links, among others, chemical, molecular modelling, bioinfor-
matic, genetic, epidemiological, and molecular diagnostic
data in order to develop prospective theragenomic informa-
tion. The system according to the invention comprises
- a master database correlating patterns of gene expression
  and genetic polymorphisms with drug-induced i. e. drug-
  related adverse effects and drug structure,
- a data-tool for structural and genetic fingerprints pre-
  dictive for adverse effects in individual patients, and
- means for coupling the master database and the predictive
  tool in such a way that electronically prospective
  theragenomic information can be developed which allows the
  safe use of a given drug or a safe drug therapy, which is,
  with high probability, free of adverse drug reactions in
  an individual patient, wherein
the master database is in a form such that data records of
the following type can be entered:
- Basic drug information such as for example information to
  intermediates, metabolites, adducts, targets, mimics,
  pathways, 2D-structures, 3D-structures and similarities.
- Clinical endpoint information such as for example drugs,
  type of endpoint, frequency.
- Drug-induced effects by genes on, as for example,
  receptors, promoters, transcription factors, responsive

elements, expression patterns, gene function, 3D-structure, adduct targets, and autoantigens.

- Drug-induced effects to allelic variants, such as for example, SNP's, splice variants, and amplifications on function(s), 3D-structure, frequencies, ethnic differences, predictive power, selectivity and sensitivity.

The object is also achieved by a Method carrying out with said system, wherein the master database is being coupled to the database of the predictive data-tool in such a way that a user of the system can develop and carry out different screening approaches either to verify the sociability of drugs for a specific selected category of patients or to search a specific drug for a selected category of patients which do not have adverse drug reactions or to make risk-analyses.

DESCRIPTION OF THE INVENTION

It is generally known that the development of most drug-related adverse effects in man is based on the genetic and epigenetic predisposition, i.e. susceptibility of each individual. This predisposition is reflected in predictive patterns of structural properties, genetic polymorphisms and gene expression profiles that correlate with the development of drug related adverse effects.

The genetic predisposition is phenotypically revealed only when the individual carrier is exposed to (the) offending agent(s) or structural mimics thereof.

According to the present invention, the master database is stored on a separate server. In accordance with the invention the system also comprises a predictive data-tool in

electronic from. In this tool the structural and genetic
fingerprints predictive for given adverse effects in individ-
ual patients due to treatment with a selected drug are
stored.

Each individual patient-specific data in reality com-
prises a set of selected yet predictive structural and
genetic information that can be presented on a gene chip to
be used in theratyping of individual patients.

This means that a given drug or a given combination of
drugs used as therapy regimen have its corresponding unique
set of patient-specific data. These data can be further clas-
sified into various subgroups as for example in subgroups de-
pendent of the sex and/or of the age of the patients or in
subgroups corresponding to clinical endpoints and/or risk
groups.

The method according the invention is characterised in
that the master database is being coupled to the database of
the predictive data-tool in such a way that a user of the
system can develop different screening approaches either to
verify the sociability of drugs for a specific selected
category of patients or to search a specific drug for a
selected category of patients which do not have adverse drug
reactions or to make risk-analyses.

Therefore, it is also part of the invention that with an
adequate tool available, theragenomics, can entirely be done
electronically.

It is another part of the invention to make available the
system, i.e. the basic database and the predictive-tool data-
base to the user via the Internet or an Intranet. For that
purpose the system further comprises means which allows the

user to follow up their screening procedures in the databases via an Internet- or Intranet-server, from where they can be called up merely by means of a login and a password.

5   The database type on which the method and system according to the invention is based is freely selectable and, for example, VISUAL FOXPRO. The same also applies to the computer operating system on which the database is based, which may be, for example, WINDOWS NT.

10   The invention will become apparent from the study of the following specification with reference to the attached drawing. In the drawing,

Figure 1 illustrates the principle of the correlation of drug-dependent data stored in the master database and in the predictive data-tool, and

Figure 2 shows a diagram illustrating the principle of the function of the system and method according to the invention.

The three main features of the invention are:

The master database:	Which is
	- an object-oriented database-system,
	- based on a knowledge management-system,
	- Internet- or Intranet-based.
The predictive data-tool(s):	Which comprises
	- structural and genetic fingerprints (information), transferable to
	- diagnostic tools (for example, gene chip arrays).

The custom services: Which is characterised by consulting
                         for example
                         - pharmaceutical industries,
                         - regulatory agencies (such as for
                           example BAG, IKS, BPharm, EMEA,
                           FDA),
                         - societies (such as for example SOT,
                           EUROTOX, others),
                         - patients, physicians, health care
                           providers,
                         - financial analysts, investors,
                           lawyers, courts and
                         - The public.

The master database correlates patterns of gene expres-
sion and genetic polymorphisms with drug-induced adverse
effects and drug structure. This database can comprise drug
specific date as follows:

Structural Chemistry   Factors such as for example 2D-and 3D-
and Genomics: structures;
                         effects to receptors; ligands;
                         metabolites; intermediates; function
                         and structure of wt-gene and allelic
                         variants gene products; chemical and
                         postranslational modifications;
                         others.

Pharmacogenetics: Factors such as for example mutated or
                         re-arranged genes:
                         e.g., CYP's; NAT-1; NAT-2; GST-_; p53;
                         Rb: WT1; BRCA1; BRCA2; VHL; APC; NF-
                         1;NF-2; MYS-1; splice variants (i.e.,
                         CD44v5, CD44v6); transcription
                         factors; responsive elements; many
                         others.

Expression genetics:	Factors such as for example over- or under-expression of unmutated or mutated genes: e.g., CYP's; p15; p 107; p300; cyclin D1 (amplification); class II cancer genes (altered in expression); regulated transcription factors; many others.
Proteomics	Factors such as for example up- or down-regulation of protein expression; posttranslational modifications; chemical adduct formation; gain of new properties through modification; others.
Epigenetic networks and Environmental factors:	Other factors such as for example DNA-methylation; signalling cascades; narangenin; bergotamine, alkaloids; retinoids; quinines; co-medications; man-made chemicals in the environment; infections; viral loads; status or type of disease.

According to the invention, the input of data into the master database is effected by data-transfer from clinical centers, i.e from clinical data networks and/or from public
5   domain, Internet and proprietor databases and/or from pharmaceutical companies and/or from bioinformatic databases. The data-transfer can ensure upon copying the data from diskettes, CD-ROM or DVD. Of course, it is also possible to transfer the data via the Internet.

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The same procedure is effective for the set up of the predictive-data-tool.

The method according the invention couples the master
15   database and the database of the predictive data-tool in such

a way that a user of the system can develop different screening approaches either to verify the sociability of drugs for a specific selected category of patients or to search a specific drug, which show no adverse drug reactions
5   for a selected category of patients, or to make risk-analyses.

Screening approaches can follow up according to the table below:

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Clinical Endpoint(s), such as, for example:	Approaches, such as, for example:
• Hepatitis C: Response to Therapy • Transplantation : Chronic rejection • Ulcerogenesis of NSAID's COX-1 / 2 • Haemolytic Anaemia • Cholestasis • Hepatitis • Thrombocytopenia • Agranulocytosis	Pharmacogenetics - Pattern of genetic polymorphism - Pattern of gene expression Biostatistics - Predictive Power - Sensitivity - Selectivity - Pattern Frequency - (Allele) Frequency - Level of confidence Molecular Modelling - Chemical structure - Structural similarity - Molecular mimicry - Homology modelling

As mentioned above it is also a part of the invention to make available the system, i.e. the basic database and the predictive-tool database, to the public via the Internet.
15   Preferred users are pharmaceutical industries, regulatory agencies, societies, patients, physicians and health care providers. Large pharmaceutical industries can use the system

for postmarketing as well as for late and early drug-development purpose. Small pharmaceutical industries can use the system for compound selection and very early drug-development purpose.

The system and method according to the invention has enormous advantages. Thus, the pharmaceutical industries can screen their new products for adverse drug reactions in a simple and secure manner. Moreover, the data of the two data-bases of the system can be relatively simply updated and can be offered to various users on a data medium or by Internet or on Intranet. All in all, the method according to the invention also simplifies the search tasks of the industries to find out possible adverse reactions of drugs in development, so that it can, with high probability, be avoided that a drug has do be withdrawn from the market because of adverse drug reactions after coming onto the market.